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L6: Entry 7 of 36 File: PGPB Mar 6, 2003

DOCUMENT-IDENTIFIER: US 20030044983 A1
TITLE: Nucleic acid transfer complexes

Detail Description Paragraph:
[0050] A "therapeutic gene" refers herein to a nucleic acid that may have a therapeutic effect upon transfection into a cell. This effect can be mediated by the nucleic acid itself (e.g., anti-sense nucleic acid), following transcription (e.g., anti-sense RNA, ribozymes, interfering dsRNA), or following expression into a protein. "Protein" refers herein to a linear series of greater than 2 amino acid residues connected one to another as in a polypeptide. A "therapeutic" effect of the protein in attenuating or preventing the disease state can be accomplished by the protein either staying within the cell, remaining attached to the cell in the membrane, or being secreted and dissociated from the cell where it can enter the general circulation and blood. Secreted proteins that can be therapeutic include hormones, cytokines, growth factors, clotting factors, anti-protease proteins (e.g., alpha1-antitrypsin), angiogenic proteins (e.g., vascular endothelial growth factor, fibroblast growth factors), antiangiogenic proteins (e.g., endostatin, angiostatin), and other proteins that are present in the blood. Proteins on the membrane can have a therapeutic effect by providing a receptor for the cell to take up a protein or lipoprotein. Therapeutic proteins that stay within the cell (intracellular proteins) can be enzymes that clear a circulating toxic metabolite as in phenylketonuria. They can also cause a cancer cell to be less proliferative or cancerous (e.g., less metastatic), or interfere with the replication of a virus. Intracellular proteins can be part of the cytoskeleton (e.g., actin, dystrophin, myosins, sarcoglycans, dystroglycans) and thus have a therapeutic effect in cardiomyopathies and musculoskeletal diseases (e.g., Duchenne muscular dystrophy, limb-girdle disease). Other therapeutic proteins of particular interest to treating heart disease include polypeptides affecting cardiac contractility (e.g., calcium and sodium channels), inhibitors of restenosis (e.g., nitric oxide synthetase), angiogenic factors, and anti-angiogenic factors.

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L6: Entry 7 of 36 File: PGPB Mar 6, 2003

PGPUB-DOCUMENT-NUMBER: 20030044983
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030044983 A1

TITLE: Nucleic acid transfer complexes

PUBLICATION-DATE: March 6, 2003

US-CL-CURRENT: 435/458

APPL-NO: 10/ 161241 [PALM]
DATE FILED: May 31, 2002

RELATED-US-APPL-DATA:
Application 10/161241 is a division-of US application 09/709656, filed November 10, 2000, US Patent No. 6458382
Application is a non-provisional-of-provisional application 60/165211, filed November 12, 1999,

[0001] This application claims priority benefit of U.S. Application Ser. No. 09/709,656 filed Nov. 10, 2000 and provisional Application Ser. No. 60/165,211 filed Nov. 12, 1999.

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L6: Entry 21 of 36 File: USPT Oct 7, 2003

US-PAT-NO: 6630448
DOCUMENT-IDENTIFIER: US 6630448 B2

TITLE: Methods of inhibiting angiogenesis with endostatin protein

DATE-ISSUED: October 7, 2003

US-CL-CURRENT: 514/12; 514/2

APPL-NO: 09/ 154302 [PALM]
DATE FILED: September 16, 1998

PARENT-CASE:
CROSS REFERENCE TO PRIOR RELATED CASES This application is a divisional application of U.S. patent application Ser. No. 08/740,168 filed Oct. 22, 1996, now U.S. Pat. No. 5,854,205 which claims priority to provisional application Serial No. 60/005,835 filed Oct. 23, 1995; provisional application Serial No. 60/023,070 filed Aug. 2, 1996; and provisional application Serial No. 60/026,263 filed Sep. 17, 1996. Each of the above-referenced applications is incorporated herein in its entirety.

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L6: Entry 32 of 36 File: USPT Oct 1, 2002

DOCUMENT-IDENTIFIER: US 6458382 B1
TITLE: Nucleic acid transfer complexes

Detailed Description Text (20):
A "therapeutic gene" refers herein to a nucleic acid that may have a therapeutic effect upon transfection into a cell. This effect can be mediated by the nucleic acid itself (e.g., anti-sense nucleic acid), following transcription (e.g., anti-sense RNA, ribozymes, interfering dsRNA), or following expression into a protein. "Protein" refers herein to a linear series of greater than 2 amino acid residues connected one to another as in a polypeptide. A "therapeutic" effect of the protein in attenuating or preventing the disease state can be accomplished by the protein either staying within the cell, remaining attached to the cell in the membrane, or being secreted and dissociated from the cell where it can enter the general circulation and blood. Secreted proteins that can be therapeutic include hormones, cytokines, growth factors, clotting factors, anti-protease proteins (e.g., alpha1-antitrypsin), angiogenic proteins (e.g., vascular endothelial growth factor, fibroblast growth factors), antiangiogenic proteins (e.g., endostatin, angiostatin), and other proteins that are present in the blood. Proteins on the membrane can have a therapeutic effect by providing a receptor for the cell to take up a protein or lipoprotein. Therapeutic proteins that stay within the cell (intracellular proteins) can be enzymes that clear a circulating toxic metabolite as in phenylketonuria. They can also cause a cancer cell to be less proliferative or cancerous (e.g., less metastatic), or interfere with the replication of a virus. Intracellular proteins can be part of the cytoskeleton (e.g., actin, dystrophin, myosins, sarcoglycans, dystroglycans) and thus have a therapeutic effect in cardiomyopathies and musculoskeletal diseases (e.g., Duchenne muscular dystrophy, limb-girdle disease). Other therapeutic proteins of particular interest to treating heart disease include polypeptides affecting cardiac contractility (e.g., calcium and sodium channels), inhibitors of restenosis (e.g., nitric oxide synthetase), angiogenic factors, and anti-angiogenic factors.

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L11: Entry 5 of 47 File: PGPB Feb 5, 2004

DOCUMENT-IDENTIFIER: US 20040023877 A1
TITLE: Angiostatin protein

Detail Description Paragraph:
[0098] The present invention includes-compositions and methods for the detection and treatment of diseases and processes that are mediated by or associated with angiogenesis. The composition is angiostatin, which can be isolated from body fluids including, but not limited to, serum, urine and ascites, or synthesized by chemical or biological methods (e.g. cell culture, recombinant gene expression, protein synthesis, and in vitro enzymatic catalysis of plasminogen or plasrnin to yield active angiostatin). Recombinant techniques include gene amplification from DNA sources using the polymerase chain reaction (PCR), and gene amplification from RNA sources using reverse transcriptase/PCR. Angiostatin inhibits the growth of blood vessels into tissues such as unvascularized or vascularized tumors.

Detail Description Paragraph:
[0110] Strategies for treating these medical problems with gene therapy include therapeutic strategies such as identifying the defective gene and then adding a functional gene to either replace the function of the defective gene or to augment a slightly functional gene; or prophylactic strategies, such as adding a gene for the product protein that will treat the condition or that will make the tissue or organ more susceptible to a treatment regimen. As an example of a prophylactic strategy, a gene such as angiostatin may be placed in a patient and thus prevent occurrence of angiogenesis; or a gene that makes tumor cells more susceptible to radiation could be inserted and then radiation of the tumor would cause increased killing of the tumor cells.

Detail Description Paragraph:
[0118] Viral vectors that have been used for gene therapy protocols include but are not limited to, retroviruses, other RNA viruses such as poliovirus or Sindbis virus, adenovirus, adeno-associated virus, herpes viruses, SV 40, vaccinia and other DNA viruses. Replication-defective murine retroviral vectors are the most widely utilized gene transfer vectors. Murine leukemia retroviruses are composed of a single strand RNA complexed with a nuclear core protein and polymerase (pol) enzymes, encased by a protein core (gag) and surrounded by a glycoprotein envelope (env) that determines host range. The genomic structure of retroviruses include the gag, pol, and env genes enclosed at by the 5' and 3' long terminal repeats (LTR). Retroviral vector systems exploit the fact that a minimal vector containing the 5' and 3' LTRs and the packaging signal are sufficient to allow vector packaging, infection and integration into target cells providing that the viral structural proteins are supplied in trans in the packaging cell line. Fundamental advantages of retroviral vectors for gene transfer include efficient infection and gene expression in most cell types, precise single copy vector integration into target cell chromosomal DNA, and ease of manipulation of the retroviral genome.

Detail Description Paragraph:
[0126] Gene regulation of angiostatin may be accomplished by administering compounds that bind to the angiostatin gene, or control regions associated with the angiostatin gene, or its corresponding RNA transcript to modify the rate of transcription or translation. Additionally, cells transfected with a DNA sequence

encoding angiostatin may be administered to a patient to provide an in vivo source of angiostatin. For example, cells may be transfected with a vector containing a nucleic acid sequence encoding angiostatin.

Detail Description Paragraph:
[0140] One example of a method of producing angiostatin using recombinant DNA techniques entails the steps of (1) identifying and purifying angiostatin as discussed above, and as more fully described below, (2) determining the N-terminal amino acid sequence of the purified inhibitor, (3) synthetically generating 5' and 3' DNA oligonucleotide primers for the angiostatin sequence, (4) amplifying the angiostatin gene sequence using polymerase, (5) inserting the amplified sequence into an appropriate vector such as an expression vector, (6) inserting the gene containing vector into a microorganism or other expression system capable of expressing the inhibitor gene, and (7) isolating the recombinantly produced inhibitor. Appropriate vectors include viral, bacterial and eukaryotic (such as yeast) expression vectors. The above techniques are more fully described in laboratory manuals such as "Molecular Cloning: A Laboratory Manual" Second Edition by Sambrook et al., Cold Spring Harbor Press, 1989. The DNA sequence of human plasminogen has been published (Browne, M. J., et al., "Expression of recombinant human plasminogen and aglycoplasminogen in HeLa cells" Fibrinolysis Vol.5 (4). 257-260, 1991) and is incorporated herein by reference The gene for angiostatin may also be isolated from cells or tissue (such as tumor cells) that express high levels of angiostatin by (1) isolating messenger RNA from the tissue, (2) using reverse transcriptase to generate the corresponding DNA sequence and then (3) using the polymerase chain reaction (PCR) with the appropriate primers to amplify the DNA sequence coding for the active angiostatin amino acid sequence.

Detail Description Paragraph:
[0176] Another kit is used for localization of angiostatin in tissues and cells. This angiostatin immunohistochemistry kit provides instructions, angiostatin antiserum, and possibly blocking serum and secondary antiserum linked to a fluorescent molecule such as fluorescein isothiocyanate, or to some other reagent used to visualize the primary antiserum. Immunohistochemistry techniques are well known to those skilled in the art. This angiostatin immunohistochemistry kit permits localization of angiostatin in tissue sections and cultured cells using both light and electron microscopy. It is used for both research and clinical purposes. For example, tumors are biopsied or collected and tissue sections cut with a microtome to examine sites of angiostatin production. Such information is useful for diagnostic and possibly therapeutic purposes in the detection and treatment of cancer. Another method to visualize sites of angiostatin biosynthesis involves radiolabeling nucleic acids for use in in situ hybridization to probe for angiostatin messenger RNA. Similarly, the angiostatin receptor can be localized, visualized and quantitated with immunohistochernistry techniques.

Detail Description Paragraph:
[0237] To construct the insert, the gene fragment encoding human angiostatin is obtained from human liver MRNA which is reverse transcribed and amplified using the polymerase chain reaction (PCR) and specific primers. The product of 1131 base pairs encodes amino acids 93 to 470 of human plasminogen. The amplified fragment was cloned into the XhoI/KpnI site of pTrcHisA, and the resultant construct transformed into XL-1B (available from Stratagene) E. coli host cells. A control clone containing the plasmid vector pTrcHisA alone was transformed inot XL-1B E. coli host cells as well. This clone is referred to as the vector control clone. Both clones were purified identically as described below.

Detail Description Paragraph:
[0258] Gene Therapy--Effect of Transfection of the Angiostatin Gene on Tumor Volume.

Detail Description Paragraph:

[0278] To localize the in vivo site of expression of angiostatin protein, total RNA from various cell types, Lewis lung carcinoma cells (mouse), T241 fibrosarcoma (mouse), and Burkitt's lymphoma cells (human), both from fresh tumor or cell culture after several passages were analysed to determine the presence of angiostatin transcripts. Northern analysis of samples showed an absence of any signal hybridizing with thn sequence from all samples except that of normal mouse liver RNA showing a single signal of approximately 2.4 kb corresponding to mouse plasminogen. Northern analysis of human samles show an absence of any signal hybridizing with human angiostatin sequence from all samples except that of normal human liver RNA showing a single signal of approximately 2.4 kb corresponding to human plasminogen.

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L11: Entry 22 of 47 File: PGPB Mar 6, 2003

DOCUMENT-IDENTIFIER: US 20030045465 A1
TITLE: Histidine copolymer and methods for using same

Summary of Invention Paragraph:
[0026] The pharmaceutical agent can be a protein, a peptide, nucleic acid, an antisense oligonucleotide, a ribozyme, an RNA-cleaving DNA oligonucleotide, a cancer chemotherapeutic agent, an infectious disease chemotherapeutic agent, a diagnostic agent, or a combination of the above. Where the pharmaceutical agent comprises a nucleic acid, such as a DNA or an RNA molecule, the nucleic acid, in one aspect, is provided as an expression vector; that is, under control of elements which can express the nucleic acid in a host cell. In another aspect, where the nucleic acid is an antisense, ribozyme, or an RNA-cleaving DNA oligonucleotide, an expression vector is not required.

Detail Description Paragraph:
[0091] The pharmaceutical agent delivery composition of the invention suitably comprises a pharmaceutical agent selected from the group consisting of a protein, a peptide, a nucleic acid, an antisense oligonucleotide, a ribozyme, an RNA-cleaving DNA oligonucleotide, a cancer chemotherapeutic agent, an infectious disease chemotherapeutic agent, a diagnostic agent, and any combination of two or more of the above.

Detail Description Paragraph:
[0092] With respect to nucleic acid delivery applications, the pharmaceutical agent suitably comprises a nucleic acid, such as DNA or RNA The nucleic acid is preferably associated with control elements to express the nucleic acid in the target cell population. The expression vector may include inducible or non-inducible promoters preceding the expressed DNA. Examples of inducible promoters include Tet, ecdysone, or steroid-metallothionine promoters. Examples of constitutive non-inducible promoters include long terminal repeat (LR), simian viral, phosphoglycerate kinase (PGK), b-actin, or cytomegalovirus (CMV) promoters. Furthermore, the promoters allow general (CMV, PGK) or specific expression (e.g. alpha fetoprotein, tyrosinase) of coding DNA. The viral or plasmid based delivery systems may contain multiple promoters to enhance transfection. Moreover, the vector DNA may include IRES (internal ribosome entry site) between different DNA coding sequences, allowing for the translation of more than one polypeptide from the same transcript. Alternatively, a plasmid or a virus can also express the pharmaceutical agent. Formulation of nucleic acid for expression in gene therapy is described extensively in the literature.

Detail Description Paragraph:
[0113] Ex vivo and in vivo gene therapy with therapeutic DNA could also be used in cancer. Gene therapy applications toward cancer include the following: 1) enhanced immunogeniticy of tumor (e.g., insert foreign antigens, cytokines, ICAMI, MHC class II and/or B7 co-stimulatory molecule genes); 2) genetically alter immune cells to increase function (e.g., cytokines, co-stimulatory molecules, and a tumor-specific T cell receptor; 3) insert suicide gene into a tumor (e.g., thymidine kinase, cytosine deaminase genes); 4) block oncogene expression (e.g. antisense K-ras, intracellular antibodies); 5) insertion of a tumor suppressor gene (e.g., p53, rb, p21, or p16 genes); 6) antiangiogenic gene therapy (e.g. angiogstatin, endostatin,

antitbrombin III, KDR, or antisense to VEGF or PDECGF genes); 7) protect tissues from the systemic toxicities of chemotherapy (e.g., multiple drug resistance type I, DNA repair enzymes, alkyltranferase, dihydrofolate reductase genes); 8) induce normal tissues to produce antitumor substances, production of recombinant vaccines for the prevention and treatment of malignancy (e.g., interferon gene); 9) local radioprotection of normal bystander tissues with antioxidant overexpression (e.g., glutathione synthetase or transferase, manganese superoxide dismutase genes; 10) insertion of genes to enhance tumor sensitivity to radiation (e.g., manganse superoxide dismutase, TNF-.alpha.); 11) transfer of genes that block expression of receptors critical for tumor cell survival (e.g., EGF, IGF-1 receptor genes); 12) transfer of genes necessary for survival (e.g., Fas or Fas ligand genes); 13) transfer of antimetastatic disease (e.g., nitric oxide synthetase); and 14) production of recombinant vaccines for the prevention and treatment of malignancy (e.g., injection of CEA, BCG, MAGE-1, tyrosinase, muc-1, Mum-1 genes).

Detail Description Paragraph:
[0161] In vivo delivery of pharmaceutical agents. The following example demonstrates that HH-K4b has utility in vivo as a carrier of low molecular weight DNA molecules in the absence of an intracellular delivery compound. In this example, the receptor of VEGF mRNA with a DNA oligonucleotide that has enzymatic activity (also called DNAzyme) (36) was targeted. The VEGF receptor is essential for tumor angiogenesis and consequently tumor growth. After breast cancer cells MDA-MB-435 cells) were injected into nude mice and the tumors grew to a visible size, the tumor was injected with the therapeutic polymer-DNA complex The tumor was injected every 5 days for a total of 5 injections. There were 4 treatment groups: 1) untreated, 2) HH-K4B carrier alone, 3) HH-K4b+DNAzyme, and 4) HH-K4b +antisense oligonucleotides. To prepare the complex for injection, 45 .mu.g of the HH-K4b polymer diluted in 150 .mu.l of water was mixed with 24 .mu.g of oligonucleotide, also diluted in 150 .mu.l of water. After formation of the complex for 2 hours, 25 .mu.l of the treatment complex was injected into each tumor. The therapeutic oligonucleotide sequence is 5'-TGCTCTCCA-GGCTAGCTACAACGA-CCTGCACCT-3'whereas the control antisense oligonucleotide sequence is 5'-TGCTCTCCA-GGCTATGTACAACGA-CCTGCA-CCT-3'. The only difference between the therapeutic DNAzyme sequence and the antisense sequences is that the nucleotides responsible for cleaving the mRNA have been altered with the antisense DNA. The tumor volume, measured before each injection, is given in the table below.

Detail Description Paragraph:
[0199] 36. Santoro, S. W., and Joyce, G. F. 1997. A general purpose RNA-cleaving DNA enzyme. Proc. Natl. Acad. Sci. USA 94, 4262-4266.

CLAIMS:

10. The pharmaceutical agent delivery composition of claim 9, wherein said nucleic acid is an antisense oligonucleotide, a ribozyme, an RNA-cleaving DNA oligonucleotide, or a combination of two or more of the above.

21. The method of claim 20, wherein said nucleic acid is an a sense oligonucleotide, a ribozyme, an RNA-cleaving DNA oligonucleotide, or a combination of two or more of the above.

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L11: Entry 41 of 47 File: USPT Dec 31, 2002

DOCUMENT-IDENTIFIER: US 6500807 B1
TITLE: Modified pectin and nucleic acid composition

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Brief Summary Text (12):
In accord with the present invention, it has been found that carbohydrates can provide a very effective delivery vehicle for DNA and other such nucleic acid materials used in gene therapy. That is, a therapeutically effective amount of a therapeutic composition of the carbohydrate and the nucleic acid material can be administered to a patient or subject having a tumor to treat the tumor by causing a reduction and/or an elimination of the tumor from the patient. In the context of this disclosure, nucleic acid materials are meant to comprise genes, plasmids containing genes, other strands of DNA, RNA, and like materials. It has been found that when nucleic acid materials are mixed with, and preferably encapsulated by, carbohydrates, these materials are protected and efficiently delivered to target cells. Multiple genes can be delivered at one time and can be delivered in a single vector or in multiple vectors encapsulated by the carbohydrates of the present invention. The carbohydrate based gene therapy materials of the present invention have been found to be effective even when administered orally, although such materials could also be delivered intravenously or by direct injection to a target tissue (i.e. a tumor).

Brief Summary Text (22):
Retroviral vectors can be constructed to function either as infectious particles or to undergo only a single initial round of infection. In the former case, the genome of the virus is modified so that it maintains all the necessary genes, regulatory sequences and packaging signals to synthesize new viral proteins and RNA. Once these molecules are synthesized, the host cell packages the RNA into new viral particles which are capable of undergoing further rounds of infection. The vector's genome is also engineered to encode and express the desired recombinant gene. In the case of non-infectious viral vectors, the vector genome is usually mutated to destroy the viral packaging signal that is required to encapsulate the RNA into viral particles. Without such a signal, any particles that are formed will not contain a genome and therefore cannot proceed through subsequent rounds of infection. The specific type of vector will depend upon the intended application. The actual vectors are also known and readily available within the art or can be constructed by one skilled in the art using well-known methodology.

Brief Summary Text (26):
While the present invention can be employed in connection with a variety of different gene therapies and/or specific genes, one particular embodiment has specific utility in cancer therapies. The tyrosine kinase gene (CHK) has been found to be an effective gene therapy material for various cancers. CHK expression has been observed in many human primary tumors including ovarian carcinoma, breast carcinoma, astrocytoma, glioblastoma, pancreatic carcinoma, lung carcinoma, liver carcinoma, and renal carcinoma The CHK gene is up-regulated in many cancers and can suppress tumor development. In some instances the gene appears to induce apoptosis. In breast cancer, the gene has been found to antagonize growth-promoting signals mediated by Src and ErbB-2 tyrosine kinases. Applicant has further found that many tumor cells have sites thereon which actively bind carbohydrates thereto, and the CHK gene, via its stimulation of the production of tyrosine kinases, causes buildup

of carbohydrate to occur on the surface of cancer cells. Based on these findings, Applicant has surmised that the CHK gene and carbohydrate materials of the present invention can interact beneficially to provide a gene therapy material for a variety of cancers. Other genes which can be used in the present invention include tumor suppressor genes including p53, angiostatic genes including angiostatin p60-hangio or endostatin p60-hendo, apoptotic genes including Bcl and Bax, and/or mixtures thereof.

Other Reference Publication (12):

Tanaka et al. "Viral Vector-targeted Antiangiogenic Gene Therapy Utilizing an Angiostatin Complementary DNA" Cancer Research 58, 3362-3369 (Aug. 1, 1998).

CLAIMS:

4. The composition of claim 1, wherein said nucleic acid material is RNA.

8. The composition of claim 1, wherein said nucleic acid material is RNA.